COMPOUNDS FOR INHIBITION OF HIV INFECTION BY BLOCKING HIV ENTRY

ABSTRACT OF THE INVENTION

A group of compounds that inhibit HIV replication by blocking HIV entry was identified. Two representative compounds, designated NB-2 and NB-64, inhibited HIV replication (p24 production) with IC_{50} values < 0.5 μg/ml. It was proved that NB-2 and NB-64 are HIV entry inhibitors by targeting the HIV gp41 since: 1) they inhibited HIV-mediated cell fusion; 2) they inhibited HIV replication only when they were added to the cells less than one hour after virus addition; 3) they did not block the gp120-CD4 binding; 4) they did not interact with the coreceptor CXCR4 since they failed to block anti-CXCR4 antibody binding to CXCR4-expressing cells; 5) they blocked the formation of the gp41 core that is detected by sandwich enzyme linked immunosorbent assay (ELISA) using a conformation-specific MAb NC-1; 6) they inhibited the formation of the gp41 six-helix bundle revealed by fluorescence native-polyacrylamide gel electrophoresis (FN-PAGE); and 7) they blocked binding of D-peptide to the hydrophobic cavity within gp41 coiled coil domain, modeled by peptide IQN17. These results suggested that NB-2 and NB-64 may interact with the hydrophobic cavity and block the formation of the fusion-active gp41 coiled coil domain, resulting in inhibition of HIV-1 mediated membrane fusion and virus entry.